L7: Entry 9 of 33 File: USPT

DOCUMENT-IDENTIFIER: US 6110483 A
TITLE: Adherent, flexible hydrogel and medicated coatings

Brief Summary Text (2):
This invention relates to coatings for biomedical devices in which an active agent is entrapped in a stabilizing polymer that provides improved bonding and flexibility. The active agent may be a hydrophilic polymer that produces a lubricious hydrogel, a bioactive agent that confers a physiological effectiveness, or a combination, so that the coating may be a hydrogel and/or a medicated coating.

Brief Summary Text (4):
Known hydrogel and medicated coatings for insertable devices have disadvantages, including poor adherence to inert polyolefin and metal surfaces, too much friction, too little permanence, and difficult or hazardous methods of application. With polyurethane-PVP coatings, little control can be exerted over the degree of lubricity and resistance to wet abrasion of the coatings, and such coatings are often unstable. PVP-cellulose ester coatings may be brittle, and are difficult to bond to certain substrates. Hydrogels can absorb several times their weight in water when placed in an aqueous environment, resulting in water penetrating to the coating/substrate interface, which makes adhesion failure a serious problem.

Brief Summary Text (5):
In order to solve these problems an improved polymer blend is needed for a coating for a medical device which may be formed as a hydrogel and/or a medicated coating, bonds well when dry, resists wet abrasion, is flexible enough to remain coherent on flexible devices, provides improved adherence to a wide variety of substrates, and can be prepared from chemically stable and biocompatible solvents.

Brief Summary Text (8):
The invention satisfies a long felt need for more flexible, adherent hydrogel and medicated coatings for insertable medical devices. The invention succeeds where previous efforts at providing such coatings have failed, despite extensive efforts in a crowded and mature art. The invention eliminates the need for cellulose esters, polyurethane, and other coating polymers employed in the prior art, with good resistance to wet abrasion, and enhanced flexibility and adhesion. The materials and methods of the invention were not previously known or suggested, and their advantages were not previously appreciated.

Brief Summary Text (9):
The invention encompasses a coating applied to a surface of a medical device, the coating comprising: (a) a stabilizing polymer selected from the group consisting of cross-linkable acrylic and methacrylic polymers, ethylene acrylic acid copolymers, styrene acrylic copolymers, vinyl acetate polymers and copolymers, vinyl acetal polymers and copolymers, epoxy, melamine, other amino resins, phenolic polymers, copolymers thereof, and combinations; and (b) an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the stabilizing polymer so as to produce a lubricious hydrogel, and a bioactive agent, and a combination; the active agent being entrapped in the stabilizing polymer such that the coating adheres to the surface when dry and wet, and remains coherent despite flexing of the surface.

Brief Summary Text (14):
The stabilizing polymer may be concentrated in an inner layer and the active agent in an outer layer. In preferred embodiments, the coating thickness is less than about 50 microns, the active agent is a hydrophilic polymer and the coating is a hydrogel, optionally with a biotctive agent.

Brief Summary Text (25):

The chemical structure and physical characteristics of hydrogels and medicated coatings for medical devices are poorly understood and difficult to predict. Research in this field depends heavily on empirical results as to the performance of particular coating compositions under relevant conditions. Thus, the special advantages of the inventive coatings could not have been appreciated from the prior art.

Brief Summary Text (27):
Thus, the structure of the coating is intermingled molecules of the polymer components and other coating components, in a homogeneous distribution with attributes of a solid phase mixture and solution. During drying, the polymers presumably become tangled together and obtain the desired characteristics of a hydrogel or stable matrix capable of sustained release of a bioactive agent. This relationship between the components is referred to as an entrapment of the active agent in the stabilizing polymer, with the result that the active agent is not solubilized or removed directly from the coating, as it would be without the stabilizing polymer, and the coating adheres to the substrate well enough to withstand dry handling and wet conditions expected in use.

Brief Summary Text (29):
The hydrophilic component is non-toxic and physiologically acceptable. It dissolves in organic solvents, and is partially or totally soluble in water. It absorbs and retains water and swells when wet in conjunction with the other coating components, absorbing at least its own weight in water, preferably more than about five times its weight, most preferably more than about ten times its weight, to produce a hydrogel that is suitably lubricious when wet. The amount and kind of hydrophilic polymer may readilyhydrophocted in conjunction with the hydrophobic polymer and hydrating agent to satisfy these criteria. Such hydrophilic polymers are well-known in the art, and a person of ordinary skill can readily find appropriate hydrophilic polymers that are compatible with the stabilizing polymer in the sense that together they form a hydrogel.

Brief Summary Text (42):
Coatings according to the invention may be prepared with polymers that lack points of reactivity, such as acrylic or styrene polymers or copolymers. Likewise, coatings may be made without cross-linking. However, with such coatings a greater coating thickness may be required or desirable than with layers made of polymers with points of reactivity and layers with cross-linking, in order to achieve a high degree of adhesion and flexibility according to the invention. For example, cross-linked coatings with polymers having reactive groups may be about two to about ten microns thick, in contrast with a coating of an acrylic styrene copolymer, with a hydrogel layer on top, and a total thickness of about 30-40 microns.

Brief Summary Text (51):
Solvents for the stabilizing and adherent polymer include organic solvents such as ketones, esters, toluene, lactones, dimethylformamide, halogenated solvents, tetrahydrofuran, dioxane, amines, glycol butyl ether, alkyl acetates, acetonitrile, and other commonly known organic solvents. The less toxic solvents are preferred. The inclusion of small amounts of hydroxyl groups such as alcohols and moisture in the solvent does not have a significant detrimental effect on the coating and method of the invention. Solvents for the hydrophilic polymer include most of the above as well as alcohols, acetic acid, and like solvents. A solvent system may be selected that is capable of dissolving all the constituents of the coating in a uniform solution, can act as a co-solvent in the coating layer and is non-toxic. If desirable, a solvent may be selected that interacts with the particular substrate surface to promote adhesion.

Brief Summary Text (55):
The coatings of the invention have beneficial characteristics for use on the surfaces of devices such as biomedical implants. The coating may be hydrophilic, absorbing water and swelling in an aqueous environment to become a hydrogel, so that the coating has lubricant properties, and is significantly more slippery when wet than when dry.

Brief Summary Text (56):
Various physiologically active agents may be incorporated into the hydrogel coating. Such agents maybe incorporated in order to ameliorate certain problems which typically occur on the surfaces of implanted medical devices. For instance, antithrombogenics such as heparin-quaternary ammonium complexes may be incorporated into the hydrogel systems. Antimicrobial agents such as various silver compounds, quaternary ammonium compounds such as benzalkonium chloride, phenol derivatives such as thymol, and antibiotics such as gentamycin, norfloxacin, and rifamycin can be incorporated into the hydrogel system. The hydrogel coatings can also be used as reservoirs for targeted drug

delivery. Materials such as DNA or anticancer agents such as merbarone or methotrexate can be incorporated.

Brief Summary Text (63):
The active solvents which are useful in the present invention may be individual solvents or solvent mixtures containing two or more solvents. In the case of solvent mixtures, one or more of the solvents in the mixture may be active while other solvent(s) in the mixture may be inactive. In any event, the solvent or solvent mixture dissolves or at least disperses the hydrophilic coating polymer and/or bioactive agent. In cases where the active agent is dispersed but not dissolved, a point is reached where the active agent goes into solution before all of the solvent has left the coating. During the phase of drying where the active agent is in solution, the solvent has also penetrated the substrate polymer(s) of the polymer surface. Thus, intermolecular mingling may take place between the substrate polymer(s) and the hydrogel polymer(s).

Brief Summary Text (65):
When tested by subjective methods the hydrogel coatings of the invention, when wet, are more slippery than wet, greased glass, and, when dry, are no more slippery than dry glass. The coatings of the invention are resistant to removal by wet abrasion as determined by running water over the coatings and rubbing between tightly gripped fingers while wet. The inventive coatings have high adherence when dry, as determined by attaching adhesive tape, pulling the tape off with a vigorous action, and then wetting the coated substrate to determine whether the taped portion retained the lubricant coating. The inventive coatings remain adherent and coherent for extended periods when stored in water, and neither peel off, dissolve, nor dissociate.

Brief Summary Text (66):
Suitable combinations of substrates, polymers, and solvents will be apparent to skilled practitioners. Generally, increasing the ratio of stabilizing polymer to water soluble polymer increases wet rub resistance and reduces lubricity. At high ratios, the hydrogel is not lubricious, and the coating can even be made to be hydrophobic. At low ratios, the hydrogel swells more in water and is less resistant to wet rub-off. The hydrogel may become impermanent or wash off easily.

Detailed Description Text (15):
The two coated samples were tested as per Example 1. The Sample A coated with the same hydrogel as Example 2 showed good wet and dry adhesion and wet peel resistance, and was lubricious. Under the same test conditions Sample B coated with the PVP-cellulose ester hydrogel solution failed the dry adhesion and wet peel tests, showing that the coatings of this invention are superior to the prior technology.

Detailed Description Text (42):
Example 9 was repeated except that the coating that was applied under the hydrogel consisted of the following:

Detailed Description Text (90):
The 20B sample (prior art technology) cracked and broke into small brittle pieces. The 20C sample (inventive technology) peeled off evenly and was very flexible. It could be bent over tightly on itself and did not crack or fracture. It remained as a continuous, rubbery film that could be stretched without breaking. Flexibility of the peeled coating without cracking is predictive of coherence and flexibility as applied to a substrate. Flexibility as opposed to cracking of a peeled coating is predictive of a decreased likelihood of coating failure especially on substrates of smaller diameter and those expected to be subjected to extensive flexing. This demonstrates superior flexibility of the instant invention technology over conventional coatings.

Current US Cross Reference Classification (4):
427/2.3

CLAIMS:

12. The coating according to claim 1, wherein the active agent is a hydrophilic polymer and the coating is a hydrogel.

applying a coating liquid comprising an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the stabilizing polymer so as to produce a lubricious hydrogel, and a bioactive agent, and a combination, and

(a) applying a coating liquid comprising a solvent capable of attacking the device surface, and an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the surface polymer so as to produce a lubricious hydrogel, and a bioactive agent, and a combination, and